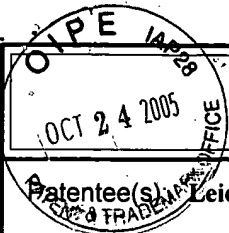


09/857960

Cgc



**TRANSMITTAL LETTER**  
**(General - Patent Issued)**

Docket No.  
LASP:111 US

Patentee(s): **Leica Microsystems Heidelberg GmbH**

U.S. Patent No.  
**6,934,022 bi**

Issue Date  
**August 23, 2005**

Title: **METHOD FOR DIFFERENTIATED INVESTIGATION OF DIVERSE STRUCTURES IN PREFERABLY BIOLOGICAL PREPARATIONS**

COMMISSIONER FOR PATENTS:

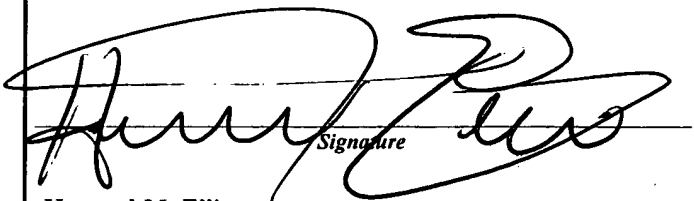
Transmitted herewith is:

- Request for Certificate of Correction
- Form PTO 1050
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- Copy of Amendment and Request for Reconsideration

**Certificate  
OCT 26 2005  
of Correction**

- ☒ No additional fee is required.
- ☐ A check in the amount of \_\_\_\_\_ is attached.
- ☐ The Director is hereby authorized to charge and credit Deposit Account as described below.
  - ☐ Charge the amount of \_\_\_\_\_
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- ☐ Payment by credit card. Form PTO-2038 is attached.

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

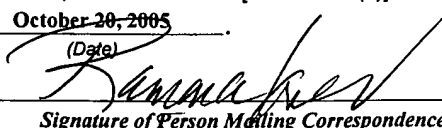
  
Signature

**Howard M. Ellis**  
**Registration No. 25,856**  
**SIMPSON & SIMPSON, PLLC**  
**5555 Main Street**  
**Williamsville, New York 14221**  
**716-626-1564- Telephone**  
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Customer No.: **24041**

cc:

Dated: **October 20, 2005**

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on	
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Signature of Person Mailing Correspondence	
<b>Ramona Jones</b>	
Typed or Printed Name of Person Mailing Correspondence	

**OCT 27 2005**



ATTORNEY DOCKET NO. LASP:111 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee(s): Leica Microsystems Heidelberg GmbH

Patent No.: 6,934,022 B1

Issued: August 23, 2005

For: METHOD FOR DIFFERENTIATED INVESTIGATION OF DIVERSE  
STRUCTURES IN PREFERABLY BIOLOGICAL PREPARATIONS

**Certificate of Mailing by First Class Mail**

I certify that this Request for Correction is being deposited on October 20, 2005 with sufficient postage with the U.S. Postal Service as first class mail under 37 C.F.R. §1.8 and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

*Ramona Jones*  
Ramona Jones

*10/20/05*  
Date

**REQUEST FOR CERTIFICATE OF CORRECTION**  
**OFFICE MISTAKE UNDER 37 CFR 1.322**

Attention Certificate of Corrections Branch  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Honorable Sir:

The above-identified patentees hereby request issuance of a Certificate of Correction of the subject patent due to a mistake by the U.S. Patent and Trademark Office (35 U.S.C. §254) in printing the patent.

Basis for the printing error (Office Mistake) can be found in a paper filed in the Office on January 5, 2005 entitled "Amendment and Request for Reconsideration" (copy attached).

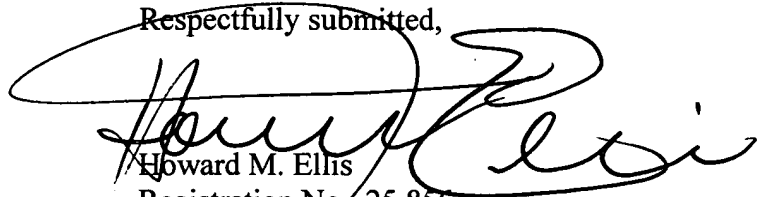
Amended Claim 57 appearing on page 6 of this paper corresponding to issued Claim 8 provided for cancellation of the term "conventional". However, Claim 8 issued with the term "conventional" in the claim, notwithstanding.

OCT 27 2005

09/147,995  
AMENDMENT  
October 20, 2005  
Page 2 of 9

It is courteously requested that this Certificate of Correction, shown on the accompanying Form PTO-1050, with the deletion of the term "conventional" in Claim 8 and occurring as a result of an Office mistake in printing the patent, be granted.

Respectfully submitted,



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Dated: 10/20/05

HME/rjl  
Enclosure

OCT 27 2005

DOC Code: COCIN

PTO/SB/44 (04-05)

Approved for use through 04/30/2007. OMB 0851-0033

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.  
(Also Form PTO-1050)

## UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 1 of 1

PATENT NO. : 6,934,022 B1

APPLICATION NO.: 09/857,960

ISSUE DATE : August 23, 2005

INVENTOR(S) : ENGELHARDT, Johann

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 6, Line 19 (Claim 8); --- delete "conventional" ---

### MAILING ADDRESS OF SENDER (Please do not use customer number below):

Howard M. Ellis - Simpson & Simpson, PLLC  
5555 Main Street  
Williamsville, NY 14221

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1.0 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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OCT 27 2005

COPY



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: J. ENGELHARDT

U.S. Patent Application No. 09/857,960

Filed: June 12, 2001

Examiner: STOCK Jr., G.

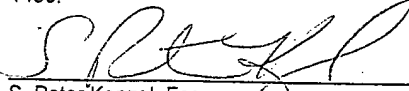
Group Art Unit: 2877

Confirmation No.: 2526

Customer No.: 24041

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I certify that this Amendment and Request for Reconsideration is being deposited on January 5, 2005 with the U.S. Postal Service as first class mail under 37 C.F.R. §1.8 and is addressed to the Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

  
S. Peter Konzal, Esq.

For: **METHOD FOR DIFFERENTIATED INVESTIGATION OF DIVERSE STRUCTURES IN PREFERABLY BIOLOGICAL PREPARATIONS**

**AMENDMENT AND REQUEST FOR RECONSIDERATION**

Mail Stop Amendment  
Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450

Honorable Sir:

This Amendment and Request for Reconsideration is being filed in reply to the Office Action dated September 8, 2004. Support for this Request for Reconsideration of the above-identified application is as follows:

**Amendments to the Claims** are reflected in the listing of the claims which begins on page 2 of this paper.

**Remarks/Arguments** begin on page 7 of this paper.

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

**Claims 1-31 (Canceled)**

**Claim 32 (Currently amended)**

A method for the differentiated examination of various structures in a biological preparation using a microscope, said method comprising the steps of:

- A) assigning particles with a specific diameter and specific characteristics to said structures;
- B) detecting said structures by detecting said particles specifically bound in or on said structures of said preparation using a light that acts on said particles, said particles possessing constant characteristics independent of the time of irradiation by said light;
- C) simultaneously recording ~~an~~ a microscopic image of said detected particles and at least one microscopic image of said structures using the microscope; and,
- D) evaluating said recorded images using digital image processing.

**Claim 33 (Previously presented)**

The method as recited in Claim 32, wherein said particles are detected by selecting a wavelength of suitable light being as a function of said diameter and of said specific characteristics of the particles such that said particles are detected on the basis of a Mie scatter occurring on said particles.

**Claim 34 (Previously presented)**

The method as recited in Claim 32, wherein said particles are detected by selecting a wavelength of a suitable light as a function of said diameter and of said specific characteristics of said particles such that said particles are detected on the basis of a plasmon signal occurring on said particles.

**Claim 35 (Previously presented)**

The method as recited in Claim 33, wherein said wavelength of said light is larger than, or is approximately equal to, said diameter of said particles.

**Claim 36 (Cancelled)**

**Claim 37 (Previously presented)**

The method as recited in Claim 32, wherein said particles are metallic particles or particles metalized on the surface.

**Claim 38 (Previously presented)**

The method as recited in Claim 37, wherein said particles are formed as ellipsoids or beads.

**Claim 39 (Previously presented)**

The method as recited in Claim 33, wherein said particles are detected through the Mie-reflexes occurring there in transmission microscope mode.

**Claim 40 (Previously presented)**

The method as recited in Claim 39, wherein said microscope is a conventional polarization transmission microscope or a confocal polarization transmission microscope.

**Claim 41 (Previously presented)**

The method as recited in Claim 33, wherein the specific detection of the particles is achieved via the Mie-reflexes occurring there in the reflection microscope mode.

**Claim 42 (Previously presented)**

The method as recited in Claim 41, wherein said microscope is a conventional polarization reflection microscope or a confocal polarization reflection microscope.

**Claim 43 (Previously presented)**

The method as recited in Claim 32, wherein said light is produced using a high-pressure lamp as a light source.

**Claim 44 (Previously presented)**

The method as recited in claim 43, wherein said light source comprises means for wavelength selection and polarization.

**Claim 45 (Previously presented)**

The method as recited in Claim 32, wherein said light is produced using a laser as a light source, said laser emitting polarized light of one wavelength.

**Claim 46 (Previously presented)**

The method as recited in Claim 32, wherein said light is produced using an optical parametric oscillator as a light source, the wavelength of said light being variable using said optical parametric oscillator, whereby a maximum Mie-signal for a specific particle type can be measured.



**Claim 47 (Previously presented)**

The method as recited in Claim 32, wherein said light is produced using a laser as a light source, said laser emitting polarized light of several different wavelengths, and means for selecting wavelengths is connected in series to said laser.

**Claim 48 (Previously presented)**

The method as recited in Claim 47, wherein said means for selecting wavelengths is integrally connected in to said laser.

**Claims 49-53 (Canceled)**

**Claim 54 (Previously presented)**

The method as recited in Claim 32, wherein said particles are coated on the surface and the coating enables a specific bonding to corresponding complementary structures of said preparation.

**Claim 55 (Currently amended)**

The method as recited in Claim 32, wherein said ~~at least one~~ microscopic ~~image~~ images ~~comprises~~ comprise a ~~conventional~~ transmitted light microscopic ~~image~~ images.

**Claim 56 (Currently amended)**

The method as recited in Claim 32, wherein said ~~at least one~~ microscopic ~~image~~ images ~~comprises~~ comprise a ~~conventional~~ reflected light microscopic ~~image~~ images.

**Claim 57 (Currently amended)**

The method as recited in Claim 32, wherein said ~~at least one~~ microscopic ~~image~~ images ~~comprises~~ comprise a ~~conventional~~ transmitted light microscopic image and a ~~conventional~~ reflected light microscopic image.

**Claim 58 (Currently amended)**

The method as recited in Claim 32, wherein said ~~at least one~~ microscopic ~~image~~ images ~~comprises~~ comprise a plurality of ~~conventional~~ transmitted light microscope images and ~~conventional~~ reflected light microscope images, wherein said ~~conventional~~ transmitted light microscope images and ~~conventional~~ reflected light microscope images are obtained under a plurality of lighting and detection angles.

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Appl. No. 09/857,960  
Amdt. dated January 5, 2005  
Reply to Office Action of September 8, 2004

**Remarks**

Review of telephonic interview of October 29, 2004

On October 29, 2004, Howard M. Ellis, Attorney of Record, and Robert C. Atkinson, who provided technical assistance on behalf of Applicant, conducted a telephonic interview with Mr. Gordon J. Stock, Jr., Examiner for the above-identified application. At the outset, Applicant would like to thank the Examiner for his generous allowance of time to discuss the merits of the case, grounds of rejection and various cited references relied on in the rejection. Applicant believes the interview was a productive and useful dialogue that clearly identified the Examiner's concerns regarding patentability.

Examiner Stock indicated United States Patent No. 6,180,415 (*Schultz et al.*) and United States Patent No. 4,752,567 (*De Brabander et al.*) formed the primary basis of his rejections. *Schultz et al.* was discussed in detail in the prior telephonic interview of June 10, 2004 between Examiner Stock, Mr. Ellis and Mr. Atkinson. The June 10 interview provided a mutual understanding that *Schultz et al.*'s disclosure was silent regarding any teaching or suggesting, as to render obvious, the concept of recording an image of the structure to which the PREs are bound. It follows that the patent is silent regarding the combination of a detection image and at least one microscopic image for subsequent evaluation by digital image processing means, according to Applicant's claims. Therefore, *Schultz et al.* fails to make out a *prima facie* case of obviousness.

Having previously discussed the merits of *Schultz et al.*'s disclosure, the teachings of *De Brabander et al.* were the focus of the telephonic interview of October 29, 2004. Examiner

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Stock expressed concern that *De Brabander et al.*'s disclosure taught capturing both a detection image and at least one microscopic image. Applicant agreed to review the patent in greater detail and would outline why it too fails to make out a *prima facie* case of obviousness. This discussion of *De Brabander et al.* is provided below.

The Rejection of Claims 32, 34, 36-38, 43-45, 47-48 and 54-58 Under 35 U.S.C. § 103(a)

Claims 32, 34, 36-38, 43-45, 47-48 and 54-58 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *Schultz et al.* in view of *De Brabander et al.*. Applicant respectfully traverses this rejection and requests reconsideration for the following reasons.

As agreed during the above-mentioned telephonic interview, Applicant is now furnishing an analysis of the *De Brabander et al.* disclosure. In view of currently amended Claim 32, the teachings of *De Brabander et al.* do not disclose each and every element of Applicant's claimed invention. *De Brabander et al.* teach a method of visualizing individual submicroscopic metal particles by subjecting the particles to specific illumination conditions and subsequently enhancing the image contrast by electronic means. More specifically, "the subject invention is concerned with visualization of single, essentially spherical, particles of submicroscopic dimensions." (*De Brabander et al.*, Col. 2, lines 51-53).

*De Brabander et al.* teach away from Applicant's invention when describing the best mode of practicing their particle visualization technique. As expressly taught in *De Brabander et al.*:

"When using the method according to the invention, and in order to distinguish the concerned metal particles to the greatest possible extent from the surrounding substrate, it will be appropriate to use a greater working aperture than required for optimal visualization of the substrate. In practice, the best results are obtained when working at full or nearly full aperture, i.e. under circumstances where the direct microscopic image has, due to its excessive brightness, almost no contrast and is for that reason completely inadequate for visual examination." (*De Brabander et al.*, Col. 5, Lines 10-20) (emphasis added).

This inadequacy is further shown in the description of the resulting image. *De Brabander et al.* describe that:

"[u]nder bright field microscopy, the spots will be dark against a bright background, while under epi-polarization microscopy, the particles will become visible as bright sparkling spots." (*De Brabander et al.*, Col. 5, Lines 24-27).

As described above, an optical system configured to perform the *De Brabander et al.* method is only capable of providing an image of the detection particles. It follows that the method cannot provide an image of the detection particles while providing an image of the structure. Therefore, in view of Applicant's amended Claim 32, *De Brabander et al.* is lacking an essential element of Applicant's claimed invention, i.e., simultaneously recording an image of the detected particles and at least one microscopic image of the structures.

Additionally, in the example provided by *De Brabander et al.*, further distinction from Applicant's invention is described. In order to discern between particles and endogenous

organelles, a practitioner of the *De Brabander et al.* method must sequentially switch between various optical setups. In contrast, Applicant's amended Claim 32 expressly states that both the detection image and at least one microscopic image of the structures are simultaneously recorded. Sequentially changing optical setups does not permit simultaneous recording of an image of the detected particles and at least one microscopic image of the structure, an essential element of Applicant's claimed invention. Hence, *De Brabander et al.* fails to make out a *prima facie* case of obviousness.

Further, in the instant Office Action, Examiner Stock concedes that *Schultz et al.* do not disclose recording an image of detected particles and at least one microscopic image of the structures to which said particles are bound. *Schultz et al.* only teach recording spectral emission characteristics, *i.e.*, recording a detection image. Although they do assert that a plurality of PREs may be obtained in a single image, an essential element of Applicant's claimed invention is still lacking, *i.e.*, simultaneously recording an image of the detected particles and at least one microscopic image of the structure. Therefore, *Schultz et al.* fail to make out a *prima facie* case of obviousness.

In order to establish a *prima facie* case of obviousness under Section 103, the references alone or in combination must teach all the elements of rejected Claim 32, which they do not. Furthermore, there is no motivation to combine *Schultz et al.* with *De Brabander et al.*, or change what is taught by these references. Therefore, it follows that Claim 32 is non-obvious in view of *Schultz et al.* and *De Brabander et al.*.

Furthermore, Claims 34, 36-38, 43-45, 47-48 and 54-58 are also non-obvious in view of *Schultz et al.* and *De Brabander et al.*, due to their dependency from Claim 32.

Withdrawal of the rejection of Claims 32, 34, 36-38, 43-45, 47-48 and 54-58 for reasons of obviousness is courteously requested.

The Rejection of Claims 33, 35 and 39-42 Under 35 U.S.C. § 103(a)

Claims 33, 35 and 39-42 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *Schultz et al.* in view of *De Brabander et al.*, further in view of United States Patent No. 6,214,560 (*Yguerabide et al.*). Applicant respectfully traverses this rejection and requests reconsideration for the following reasons.

The teachings of *Yguerabide et al.* have the same deficiencies as those of *Schultz et al.* and *De Brabander et al.*. In fact, in this instance, the patent teaches away from Applicant's invention. Similar to *De Brabander et al.*, "[t]he [*Yguerabide et al.*] method and associated apparatus are designed to maximize detection of only scattered light from the particles and thus is many times more sensitive than use of fluorophores, or the use of such particles in methods described above." (*Yguerabide et al.*, Col. 10, Lines 12-16). By optimizing their system for the maximum detection of only scattered light, *Yguerabide et al.* sacrifice the capability to record useable images of types other than scattered light. Hence, the method and apparatus would not be appropriate to record a microscopic image of the structures in addition to recording an image of the detection particles for which the invention is optimized. As in *Schultz et al.* and *De Brabander et al.*, *Yguerabide et al.* is lacking an essential element, *i.e.*, simultaneously recording

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an image of the detected particles and at least one microscopic image of the structures to which the detected particles are bound.

As explained above, in order to establish a *prima facie* case of obviousness under Section 103, the references alone or in combination must teach all the elements of rejected Claim 32, which they do not. Furthermore, there is no motivation to combine *Schultz et al.* and *De Brabander et al.* with *Yguerabide et al.*, or change what is taught by these references. Therefore, it follows that Claim 32 is non-obvious in view of *Schultz et al.* and *De Brabander et al.*, and further in view of *Yguerabide et al.*.

As Examiner Stock has indicated, dependent Claims 33, 35 and 39-42 contain all the limitations established in independent Claim 32, due to their dependency therefrom. Therefore, Claims 33, 35 and 39-42 are also non-obvious in view of *Schultz et al.* and *De Brabander et al.*, and further in view of *Yguerabide et al.*, due to their dependency from Claim 32.

Withdrawal of the rejection of Claims 33, 35 and 39-42 for reasons of obviousness is courteously requested.

#### The Rejection of Claim 46 Under 35 U.S.C. § 103(a)

Claim 46 was rejected under 35 U.S.C. § 103(a) as being unpatentable over *Schultz et al.* in view of *De Brabander et al.*, further in view of United States Patent No. 6,214,560 (*Yguerabide et al.*), and further in view of United States Patent No. 4,169,676 (*Kaiser*). Applicant respectfully traverses this rejection and requests reconsideration for the following reasons.



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As Examiner Stock has indicated, dependent Claim 46 contains all of the limitations established in independent Claim 32, due to its dependency therefrom. As previously mentioned, Claim 32 is non-obvious in view of *Schultz et al.* and *De Brabander et al.*, and further in view of *Yguerabide et al.*. Since *Kaiser* does not teach the missing element, *i.e.*, simultaneously recording a detection image and at least one microscopic image, for all the above-mentioned reasons and due to its dependency from Claim 32, it follows that Claim 46 is also patentable over *Schultz et al.* in view of *De Brabander et al.*, further in view of *Yguerabide et al.*, and further in view of *Kaiser*. Accordingly, withdrawal of the rejection of Claim 46 under 35 U.S.C. § 103(a) would be entirely appropriate.

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Ampt. dated January 5, 2005  
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### Conclusion

For all the reasons outlined above, Applicant respectfully submits that the amended claims are patentable over the cited references and in condition for allowance, which action is courteously requested. However, in the event of any remaining issues, it is courteously requested that Examiner Stock contact the undersigned attorney of record.

Respectfully submitted,



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Dated: January 5, 2005